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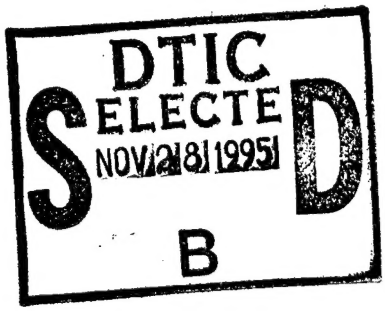

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13. ABSTRACT *(Maximum 200 words)*

The purpose of this project is to identify genes other than BRCA1 responsible for inherited predisposition to breast cancer, to identify critical mutations, to evaluate the frequency of inherited mutations in these genes among breast cancer patients from the general population, and to determine the role of somatic mutations in these genes in malignant breast tumors. The patient materials are kindreds with at least four cases of breast cancer, in whom disease is not linked to BRCA1. Twenty- one families have been sampled, lymphocyte lines established, and linkage evaluated at multiple chromosomal locales. Linkage analysis of these kindreds reveals convincing linkage to BRCA2 in three families and to the estrogen receptor in three other families. Five other candidate chromosomal regions have been screened as well. Probands from 139 other high-risk kindreds have been contacted. Of these families, 21 will be informative for linkage. Sampling of these 21 extended families is in progress. This will bring the cohort to 42 families in all.

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Mary Claire Rueg — 8/14/95

PI - Signature — Date

Genetic alterations in familial breast cancer: Mapping and cloning genes other than BRCA1

Annual report for the period August 15, 1994-August 14, 1995

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Introduction

Breast cancer is the most common malignancy among women, with a cumulative risk of 12.6%, or one in eight, by age 85 for a girl born in 1990 (American Cancer Society 1994; California Department Health Services 1994). The existence of a gene or genes responsible for inherited predisposition to breast and ovarian cancer was suggested more than a century ago (Broca 1886) and supported by a vast epidemiological literature for the past 70 years (e.g. Lane-Clayton 1926; Jacobsen 1946; Penrose et al. 1948; Macklin 1959; Anderson 1972; Bain et al. 1980; Schwartz et al. 1985; Newman et al. 1988; Claus et al. 1991). Segregation analysis of a population-based series of families (not selected for family history) indicated that highly penetrant autosomal dominant susceptibility genes were responsible for 5 to 10% of all breast cancer (Newman et al. 1988; Claus et al. 1991) and ovarian cancer (Schildkraut et al. 1989), and that approximately 1 in 200 women in the general population would develop breast cancer as the consequence of a predisposing mutation in one of these genes (Newman et al. 1988; King et al. 1993).

The existence of one gene predisposing to breast and ovarian cancer, BRCA1, was proven by linkage analysis five years ago (Hall et al. 1990) and confirmed with odds $>10^{26}$:1 (Narod et al. 1991; Easton et al. 1993). In the high-risk families evaluated for linkage, women who inherited a BRCA1 mutation had >80% lifetime risk of breast cancer and were at increased risk for ovarian cancer (Newman et al. 1988; Easton et al. 1993; Ford et al. 1994). BRCA1 was recently isolated by positional cloning (Miki et al. 1994; Futreal et al. 1994) and inherited BRCA1 mutations rapidly identified (Miki et al. 1994; Futreal et al. 1994; Castilla et al. 1994; Friedman et al. 1994; Simard et al. 1994).

BRCA2, a second breast cancer susceptibility gene, has been mapped to chromosome 13q12 (Wooster et al. 1994). Families with breast cancer linked to BRCA2 are distinguished by a high incidence of male breast cancer. Risk of breast cancer among males predicted from linkage analysis to carry BRCA2 mutations is 6% by age 70; inherited mutations in BRCA2 may be involved in 15% of all male breast cancer. Risks of female breast cancer are similar for BRCA1 and BRCA2. Both ovarian and prostatic cancer, and possibly ocular melanoma, are also at increased frequency in BRCA2 families (D Goldgar, personal communication).

BRCA1 is responsible for a higher proportion of inherited breast and ovarian cancer than is BRCA2, at least in the populations studied so far.

Among approximately 200 families with at least 4 cases of breast cancer, evaluated in various laboratories, ~50% of families have mutations in, and/or convincing linkage to, BRCA1; ~30% appear linked to BRCA2; and ~20% are not (yet) explained by either BRCA1 or BRCA2. In the subset of these families with both ovarian and breast cancer, 75% are attributable to BRCA1, 23% to BRCA2, and only one family appears as-yet-unexplained. Of course, some "unexplained" families may actually carry BRCA1 and/or BRCA2 mutations, but appear unlinked to either locus because the number of noninherited cases (i.e. phenocopies) is high. Other "unexplained" families may reflect another BRCA locus. In our series, breast cancer in two extended families not linked to BRCA1 or BRCA2 is coinherited with the estrogen receptor (Zuppan et al. 1991; see also Body of Report). The total lod score is 3.7 (1.8 and 1.9 for the two families), but no functionally significant mutations in the estrogen receptor coding sequence have been found thus far in either family.

At least two other genes--P53 and the androgen receptor--are also responsible for inherited predisposition to breast cancer in families. Mutations in P53 lead to multiple cancers in families with Li-Fraumeni syndrome, including breast, childhood leukemia, brain, and sarcoma (Malkin et al. 1990). Mutations in the X-linked androgen receptor lead to breast cancer among men with the rare Reifenstein syndrome (Wooster et al. 1992).

Breast cancer risk may also be influenced by more common alleles of other loci conferring moderate risk. Epidemiologic studies have suggested that carriers of mutations in the ataxia telangiectasia (AT) gene are at increased risk of breast cancer (Swift et al. 1991; Borreson et al. 1990), and the proportion of breast cancer attributable to AT carrier status is estimated at 3.8% (Easton 1994). Now that AT has been cloned (Savitsky et al. 1995), it will be possible to test this hypothesis directly.

Other epidemiologic studies suggest that inherited mutations in the HRAS1 minisatellite locus are associated with increased risk of breast cancer, as well as of other common cancers. Inherited mutations in the HRAS1 minisatellite lead to a large number of individually rare alleles, each derived from one of four common progenitors. Although the relative risk of cancer associated with carrying a rare allele at this locus is only 2.0, the aggregate frequency of rare alleles leads to an attributable risk of ~9% of breast cancer in the population as a whole (Krontiris et al. 1993). The mechanism underlying the increased risk remains unknown.

Body of report

High-risk breast cancer families were drawn from two sources. The first series are 20 families from our ongoing linkage studies. In these families, four or more relatives developed breast cancer, but breast cancer was not linked to BRCA1 and no mutations in BRCA1 were detected in the families. The breast cancers present in each of these families are shown in Table 1. Linkage results for BRCA2, the estrogen receptor, chromosome 3p, 8p12-q12, 11q23, 12q, and 16q24 are shown in Table 2.

Table 1. DAMD17-94-J-4307: Characteristics of families with 4+ breast cancers not linked to BRCA1

Family	Breast cancers				Ovarian or
	All breast	Female < 50	Female > 50	Male breast	fallopian tube
8	4	1	3		
9	14	6	8		
10	5	3	2		
11	7	3	4		
13	7	4	3		
15	5	2	3		
16	8	3		5	
17	4	2	2		
18	5	1	4		
19	9	5	3	1	
20	6	1	5		
22	8	1	7		
23	5	2	3		
26	11	7	4		1
33	5	2	3		1
65	5	4	1		
68	5	2	3		
87	5	4	1		2
90	9	8	1		
91	7	2	5		
94	5	3	2		
99	6	2	3	1	4

Table 2. DAMD17-94-J-4307: Linkage results on candidate chromosomes for breast cancer families not linked to BRCA1

Family	BRCA2	ESR	3p	8p12-q12	11q23	12q	16q24
8	linked (<1.0)	possible			not linked	not linked	possible
9	linked (1.40)	not linked	not applicable	not applicable	not applicable	not applicable	not applicable
10	not linked	not linked	not linked	not linked	not linked	not linked	not linked
11	not linked	not linked	not linked	possible	not linked	linked	not linked
13	not linked	linked (1.92)			not linked	not linked	
15	not linked	not linked			not linked	not linked	
16	linked (1.84)	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable
17	recheck	not linked					
18	not linked	not linked			not linked	possible	linked
19	not linked	not linked			not linked	not linked	
20	not linked	possible			not linked	possible	
22	not linked	linked (1.85)	not linked	not linked	not linked	not linked	
23	not linked	not linked			not linked	not linked	possible
26	not linked	possible					
33	not linked	not linked					
65	not linked	not linked			possible		possible
68	not linked	uninformative			not linked	not linked	possible
87	not linked				not linked	not linked	
90	not linked	not linked	not linked	not linked	not linked	not linked	not linked
94	linked (<1.0)						
99	linked (1.09)	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable

A second series of families has also been developed, based on probands who reported four or more living women in their families with breast cancer. Each participant signed informed consent prior to interview or sampling by our lab.

Each participant provided names, relationships, cancer sites, and ages at cancer diagnosis of their affected relatives. Probands were asked to provide samples of their blood, and affected family members were contacted and invited to participate. In order to contact family members, probands released their relatives' contact information. Often the probands first contacted their relatives, then after permission was given, they released the contact information to our interviewers. Our lab then contacted the relatives, by letter and then by telephone. The relatives were informed of the study by the researchers in a similar manner to the probands. If the relatives were able and willing to participate, they were sent blood collection kits identical to the kits sent to the probands.

Each woman was asked to provide 35 ml blood. Sample collection involved either sampling in person by our staff or sending blood collection kits to the participant being sampled. Each blood collection kit contained a letter from the researchers outlining the goals of the study, a list of rights of medical research subjects, procedures for drawing and packing blood samples, a sheet to document the time and place of the blood draw, a consent form for the study, and a permission form for the release of pathology reports. Upon receipt of the blood samples, lymphocyte lines were established for each individual.

The following are the results of contacting the 139 women from families with four or more affected relatives who completed the original questionnaire:

21	blood sample collected from proband; linkage family
28	blood sample collected; family not informative or unavailable
67	family not informative or not available; no blood sampled
16	proband refused or unable to participate
5	unable to locate
2	deceased
139	total

When these 21 high-risk families are sampled, the total cohort of high-risk families will number 42.

Conclusions

The following activities will be carried out in the following year:

1. Families linked to BRCA2 will be evaluated for informative meiotic recombination events. When BRCA2 is cloned, mutations in these families will be screened.

2. The estrogen receptor gene will be screened for mutations in the families linked to ESR.

3. Sampling will be completed on the additional linkage families and cell lines established. Families will be screened for linkage to BRCA1. Families in that group will be included in studies of BRCA1 mutations (supported elsewhere) and excluded from this series.

4. Linkage analyses will continue for the candidate chromosomal regions reported in table 2, both for the families listed in tables 1 and 2 and for the new series.

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